UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/703,350 | 10/31/2000 | Fuad Mchraban | 10716-15 (CURA-90/P1891R1 | 3065 |

26263 7590 03/05/2004

SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

| EXAMINER | |
|---|---|
| NICKOL, GARY B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 22 |

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/703,350 | MEHRABAN ET AL. | |
| | Examiner | Art Unit | |
| | Gary B. Nickol Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *1-55 and 58-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03-23-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

Re: Mehraban *et al.*

Date of priority: November 01, 1999

Claims 1-68 are pending.

Claims 1-55, 58-68 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 56-57 are currently under consideration.

The Election filed August 6, 2003 (Paper No. 20) in response to the Office Action of August 05, 2002 is acknowledged and has been entered. (It is noted that the petition to revive this application was granted on February 11, 2004).

Applicants have initially requested clarification of the Restricted groups (page 6) in that the numbering of groups is one too many based on the total number of PA molecules of 27. Applicants note, for example, that Groups 28-55 actually contains 28 groups, not 27. Applicants are correct. The examiner apologizes for the apparent oversight in numbering. For clarification purposes, applicants have proposed to retain the numbering as provided in the Restriction Requirement, assuming that the 28$^{th}$ group in each set does not correspond to any PA sequence. This proposal has been considered and is found persuasive. Applicant is reminded that any future group election must include the identity of the PA sequence by SEQ ID NO: as per the restriction requirement on page 2, of Paper No.12.

Applicant's traversal appears to be on the grounds that the office has not provided reasons and/or examples to support the conclusion that the identified groups are independent or distinct. In the instances of products or methods, applicants argue (pages 5 and 6) that the Office has failed to provide examples to illustrate the restriction and that the Office has made a simple assertion without support. Applicants further argue that where the inventions are related as products and processes of use (pages 6-7), the Office has not provided an explanation for how the products, as claimed, can be used in the process, i.e. affinity chromatography. These arguments have been considered but are not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 12. Furthermore, the reasons for restricting the Groups were clearly set forth in Paper No. 12, page 10. It is further noted that the restriction guidelines (MPEP 803.01) only require that the Office provide reasons and or examples, not both reasons and examples to support the restriction. Furthermore, when related inventions as claimed are shown to be distinct, the reasons for restriction may include separate classifications or different fields of search (MPEP 808.02) as indicated in Paper No. 12. Since the inventions are classified differently, it necessities different searches in the literature. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

Applicants further argue (page 7) that nowhere is the distinctness of the 27 PA sequences alleged. This argument has been considered but is not found persuasive. The distinctness of the

27 sequences was set forth on page 2 wherein the Office alleged that each PA molecule represented an independent and or distinct molecule. Applicants further traversed the species requirement (applicant's elected the species of an angiogenic agent) because the election of species is for search purposes only and that the burden rests upon the Office to demonstrate that species are patentably distinct. This argument has been considered but is not found persuasive. It is maintained that the species are patentably distinct for the reasons set forth in Paper No. 12, page 11. The Action clearly set forth that each species represented separate and distinct molecules with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

***Specification***

The specification is objected to on page 7, under the figure description for Figure 32, as the Figure discloses amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs:. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where

applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d) (see attached Notice to Comply).

***Claim Objections***

Claim 57 is objected to for reciting various therapeutic molecules (i.e. PA polypeptides, PA agonists, and PA antagonists) which are drawn to non-elected inventions. This objection can be obviated by amending the claims to the elected invention: an anti-PA23 antibody.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 57 is rejected as vague and indefinite for reciting the term "PA" as the sole means of identifying the claimed molecule. As the elected invention is drawn to PA23, the specification refers (pages 11 and 25) to PA23 as a "stanniocalcin precursor" with an accession number: U25997. However, it is well known in the art that accession numbers can be altered, deleted, amended, or revised over time by various inventors. Hence, one of ordinary skill in the art would not be able to identify the scope of the claimed subject matter. Furthermore, the use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify the claimed PA molecule by a sequence identifier, e.g., SEQ ID NO. Applicants are reminded that

the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of inhibiting angiogenesis in a mammal comprising administering to the mammal a therapeutically effective amount of an anti-PA antibody; more specifically, wherein the PA antibody targets "PA23" or a stanniocalcin polypeptide.

The claimed invention is not enabled because there is insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed.

The specification teaches (page 25) that the stanniocalcin precursor is a secreted glycoprotein that is "upregulated in endothelial cells differentiating into tube-like structures" which suggests that stanniocalcin might be involved in endothelial tube formation. The disclosure postulates that that since stanniocalcin is a secreted hormone, the existence of a receptor for stanniocalcin may be used as a target to block tube formation.

However, one cannot extrapolate the teachings of the specification to the scope of the claimed subject matter because the claims are broadly drawn to methods of administering an anti-PA23 (anti-stanniocalcin) antibody in a mammal to inhibit angiogenesis. However, it cannot be predicted from the information in the disclosure that the inhibition of the biological effect between the stanniocalcin glycoprotein and its receptor would effectively inhibit angiogenesis. The fact that the gene encoding the stanniocalcin protein is up-regulated under tube-forming conditions is insufficient evidence of the gene's and or encoded polypeptide's biological effect. Many genes are up-regulated under many different physiological processes, and it cannot be determined whether this gene directly or indirectly stimulates angiogenesis. Further, the increase in RNA content as shown in Figure 23 is insufficient proof that the corresponding amounts of protein are produced. Those of skill in the art, recognize that expression of mRNA, specific for a

tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. There are many steps in the pathway leading from DNA to protein, and all of them can in principle be regulated. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Lewin, B. also teaches (Genes VI, Oxford University Press, Inc., NY, Chapter 29, 1997) that a major control point for genes exists during the initiation of transcription by the interaction of the RNA polymerase with its promoter. Concurring with Alberts *et al.*, Lewin further acknowledges downstream control of gene expression since translation of mRNA in the cytoplasm is also a point of control. Lewin also acknowledges that control of gene expression can occur at multiple stages and that production of RNA cannot inevitably be equated with production of protein. Also, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, in-vivo correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic/therapeutic efficacy with any reasonable degree of predictability. In the instant case, applicants have not sufficiently demonstrated that the gene and or its encoded polypeptide is directly involved with angiogenesis and or shown the inhibition of angiogenesis with an antibody that is specific for stanniocalcin. For example, the use of therapeutic antibodies to treat cancer is rather unpredictable, the parallel being that

angiogenesis contributes to the vascularization and thus growth of tumors. Jain (Scientific American July 1994), discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, Dillman (Annals of Internal Medicine, Volume 111, pages 592-603, 1989) summarized (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Further, the disclosure provides no objective evidence or working examples to lend one of ordinary skill in the art a reasonable expectation of success to inhibiting angiogenesis *in vivo*. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the therapeutic use of antibodies administered to a mammal. In the

instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

Claim 55 is further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the written description is not commensurate in scope with the claims drawn to a genus of therapeutic compositions that inhibit angiogenesis.

A description of a genus of therapeutic compositions may be achieved by means of a recitation of a representative number of molecules, defined by structure, falling within the scope of the genus. However, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of therapeutic compositions that would distinguish the claimed compositions from other molecules that do not have the claimed biological properties. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of antagonists, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 56 is rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,733,876 (O'Reilly *et al.*, March 31, 1998).

O'Reilly *et al.* teach a method of inhibiting angiogenesis in a mammal comprising administering to the mammal a therapeutically effective amount of a therapeutic composition that inhibits angiogenesis (column 35).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.

Primary Examiner
Art Unit 1642

GBN

GARY NICKOL
PRIMARY EXAMINER